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REOPRO REMOVAL DURING CARDIOPULMONARY BYPASS USING A HEMOCONCENTRATOR

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ReoPro (abciximab) is the Fab fragment of a monoclonal antibody raised in mice against platelet glycoprotein IIb/IIIa complex (Gp11b-IIIa) that is present on the surface of platelets. Administration of this monoclonal antibody fragment results in almost total inhibition of platelet aggregation.[1] ReoPro has proved to be a major advance in the field of interventional cardiology, especially during coronary angioplasty and coronary stenting. Unfortunately, some patients treated with ReoPro remain unstable or develop unstable angina after intervention. Cardiac surgery is then dangerous because of the excessive bleeding that may occur in patients who have received ReoPro.[2,3] Since the bleeding that can occur can be so catastrophic that patients have died as a result, patients may be turned down by cardiac surgeons, or not referred at all.

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Manufacturer guidelines (Eli Lilly and Company, Ltd) recommend that any patient undergoing surgery after the administration of ReoPro should receive 10 units of platelets to absorb free ReoPro in the plasma. The transfusion of this large number of platelets is not only costly but also associated with significant side effects. At some smaller surgical units, sufficient platelets may simply not be available at short notice. Scattered case reports of successful cardiac surgery after the administration of ReoPro are in the literature, but none of the papers note that platelet function tests were performed to confirm that the dose of ReoPro administered to their patients was sufficient to significantly alter platelet aggregation.

Because ReoPro has a molecular weight of 50 kd, we speculated that it might be possible to remove free ReoPro from the circulation by using a hemoconcentrator during cardiopulmonary bypass. This would, of course, be unlikely to reverse the effect of ReoPro on the patient's existing platelets, but it would change the purpose of the platelet replacement from one of primarily absorbing free antibody to one of providing adequate hemostasis. This would have enormous implications to the current practice in cardiac surgery with regard to patients who have received ReoPro,[4,5] in that significantly fewer platelets would be required.

Methods. A standard cardiopulmonary circuit was estab-

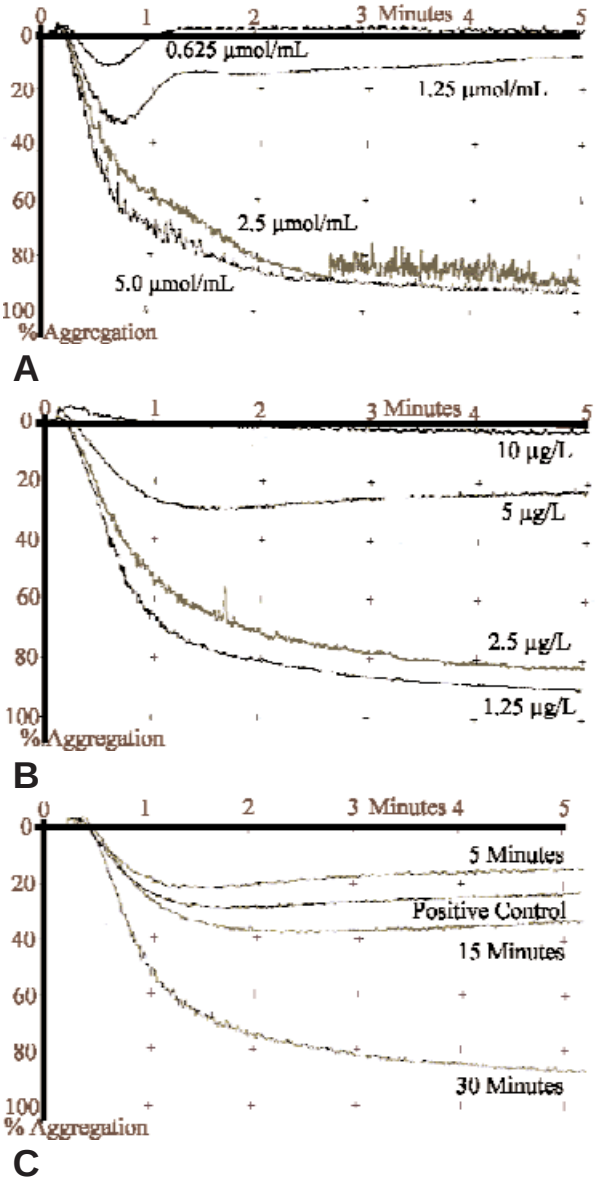

Fig 1. A, Platelet aggregation over time, with ADP concentrations from 0.625 to 5 µmol/mL. **B,** Platelet aggregation over time, with ReoPro concentration from 1.25 to 10 µg/L. **C,** Platelet aggregation over time, with time after initiation of bypass (ADP 5 µmol/mL final concentration). It can be seen that effective inhibition of platelet aggregation, due to RepPro removal, in response to 5.0 µmol/mL ADP is lost by 30 minutes. The data shown above were obtained from experiments using saline solution as the pump prime. The results obtained by using blood as the pump prime were identical.

lished by using the Stockert cardiopulmonary bypass machine (Stockert Instrumente GMBH, Munich, Germany) (n = 3). Pressure was monitored with a Tycos gauge (Tycos Instruments, Inc, Arden, NC), and nonpulsatile flow was used. A Bard hemoconcentrator type HC70 (Bard Vascular Systems Division, Haverhill, Mass) was used in line to remove the ReoPro. An Avecor cardiovascular cardiotomy/venous reservoir with filter was used (Avecor Cardiovascular, Inc, Plymouth, Minn). The pump prime, 1.5 L total, consisted of normal saline solution (n = 1) or packed red cells and normal saline solution (starting hemoglobin value 8.0 g/dL, n = 2), with added ReoPro such that the final concentration was 10 µg/L. One hour of in vitro bypass was performed, with circulating prime sampled before, 5 minutes after initiation of in vitro bypass, and then at 15-minute intervals up to 60 minutes. The in vitro bypass was performed with a mean line pressure of 70 mm Hg, which equated to a hemoconcentrator flow of approximately 1.1 L/min. The experiment was conducted at a temperature of 28°C.

ReoPro levels were assayed by means of platelet function tests on freshly prepared platelets, compared with a standard curve. A standard laboratory protocol was adhered to, using ADP for platelet stimulation and a Clandon Aggrecorder II (YSI Ltd, Farnborough, UK) for measuring aggregation. ADP has previously been shown to return the most reproducible platelet function tests after ReoPro administration.

The normal dose of ReoPro administered to patients is 0.15 to 0.3 mg/kg body weight, which corresponds to 10.5 to 21 mg in a 70-kg patient. Since the average blood volume of a 70-kg adult is 2.5 L, and the minimum pump prime during cardiopulmonary bypass is 1.5 L, the effective circulating volume in patients connected to the bypass circuit is 4 L, resulting in a final ReoPro concentration of between 2.625 and 5.25 µg/L. We used a pump prime concentration of 10 µg/L because the samples were diluted 2-fold in the platelet aggregation assay, thus resulting in the usual pharmacologic concentration.

Results. In initial experiments we established the conditions for measuring platelet aggregation by using an aggregometer. As shown in Fig 1, *A*, optimal platelet aggregation was observed by using ADP at a concentration of 5.0 µmol/mL, and this concentration was therefore adopted for further studies. Furthermore, a dose-response titration of ReoPro showed inhibition of platelet aggregation between 1.25 and 10 µg/L, with complete inhibition at the highest concentration (Fig 1, *B*).

To determine whether hemoconcentration could affect the functional activity of ReoPro, we mixed platelets in PRP 1:1 with the priming solution at various times after initiation of simulated bypass. As shown in Fig 1, *C*, effective inhibition of platelet aggregation in response to 5.0 µmol/mL ADP was lost by 30 minutes. Similar results were obtained by using 10.0 µmol/mL ADP (not shown).

Discussion. The results we have obtained, using a highly sensitive and clinically relevant assay, prove the principle that ReoPro can be removed from a cardiopulmonary bypass circuit by using a hemoconcentrator. Patients who undergo urgent cardiac surgery after ReoPro administration constitute a very high risk group. Removal of the ReoPro may result in a substantial decreased risk of bleeding during and after cardiac surgery.

The main use for our method of ReoPro elimination is obviously during cardiopulmonary bypass, but there could be other uses. For post–interventional cardiology patients who

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have received ReoPro and who subsequently have intracranial, retroperitoneal, or gastrointestinal bleeding, management becomes difficult; there is a natural hesitancy to reverse anticoagulation by provision of clotting factors in a patient who needs anticoagulation from the cardiac point of view. Because hemofiltration is easily carried out at the bedside, this could provide an avenue of treatment in a difficult and potentially hazardous situation.

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